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Development of Pyrimidine Derivatives as Selective Cox-2 Inhibitors

[1]Prafulla B. Choudhari, [1]Swapnil D. Jadhav, [1]Rakesh P. Dhavale,
[1]Manish S. Bhatia, [1]Suhel S. Shaha, [1]Kundan B. Ingale and [3]Neela M. Bhatia

[1]Department of Pharmaceutical Chemistry,
Bharati Vidyapeeth College of Pharmacy, Kolhapur 416013 (MS) India
[2]Department of Pharmaceutics,
Bharati Vidyapeeth College of Pharmacy, Kolhapur 416013 (MS) India
[3]Department of Quality Assurance,
Bharati Vidyapeeth College of Pharmacy, Kolhapur 416013 (MS) India

Abstract: Different series of 3,6- and 4,5- disubstituted 1,2,3,4-tetrahydropyrimidine derivatives were synthesized and screened for their *in-vitro* COX-1 and COX-2 inhibition activity. The selectivity index was determined from the results of *in-vitro* COX-1 and COX-2 activities. The data set was employed for QSAR analysis on Vlife Sciences MDS 3.5. The molecules were divided into training set and test set based on activity. The activity of the molecules of test set was predicted according to the QSAR equation fit. The outcomes of QSAR studies indicate that hydrophilic nature of compounds lead to selective COX-2 inhibition *in-vitro*.

Key words: Tetrahydropyrimidine · Anti-inflammatory · COX-1 · COX-2, QSAR

INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutics, primarily for the treatment of pain and inflammation, especially arthritis. The overall worldwide production of about 50,000 tons a year reflects the importance of this substance even today [1]. It is well-documented that non steroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory and analgesic effects through the inhibition of prostaglandin (PG) synthesis, by blocking cyclooxygenase (COX) activity. Two isoforms of the COX enzyme, COX-1 and COX-2, with their functional roles in the maintenance of normal homeostasis and induction of inflammation at inflammatory sites, respectively, were identified early in the past decade [2-4]. In the past decades, tetrahydropyrimidine derivatives have been shown to exhibit important pharmacological properties [5-12]. Hear we report the synthesis screening and QSAR studies of substituted 1,2,3,4-tetrahydropyrimidine derivatives (Figs 1 and 2).

All the compounds were screened for *in vitro* COX 2 inhibitory activity. QSAR analysis was performed to identify the structural features necessary for the *in vivo* activity. Toxicity studies were also performed for the synthesized derivatives.

Experimental: Melting points of synthesized compounds were determined by an open capillary method and are uncorrected. Analytical TLC was performed on Silica gel-G using Chloroform/ Ethanol(60:40) and as mobile phase. The IR (KBr) spectra were recorded on a Jasco- FTIR 4100 instrument. The ^{1}H NMR spectra of the compounds were recorded on 400 MHz Varian NMR. The solvent used was DMSO. The synthesized series was subjected to QSAR studies using Vlife MDS 3.0 running on P-IV processor. Various substitutions done on the pyrimidine ring are shown in Table 1.

Step-I:Synthesisof5-Carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydro Pyrimidine: (1A)[13]: A mixture of ethyl cyanoacetate (0.01 mol), aldehyde (0.01 mol) and thiourea (0.01 mol) in ethanol (20 ml) containing potassium carbonate (0.01 mol) was heated under reflux for 5 hrs. The potassium salt of product, which is precipitated during reaction, was collected and washed with e thanol

Corresponding Author: Manish S. Bhatia, Department of Pharmaceutical Chemistry,
Bharati Vidyapeeth College of Pharmacy Kolhapur 416013 (MS) India,

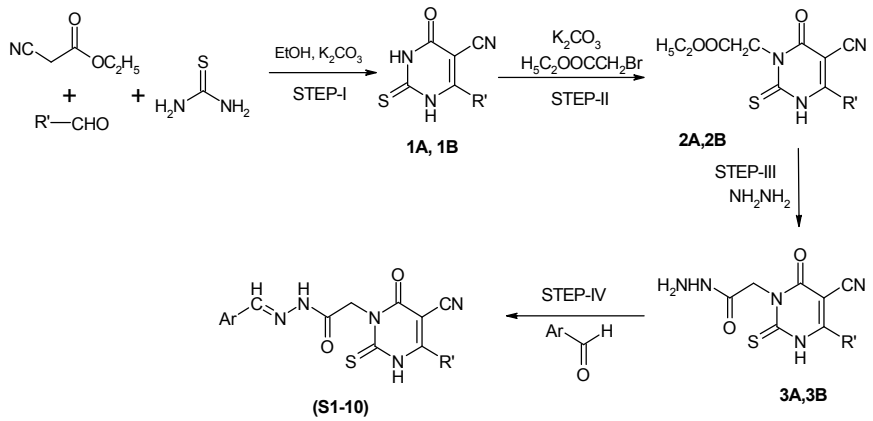

Fig. 1: Scheme for synthesis of 5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4 tetrahydropyrimidin-3-yl] ethanoic acid arylidinehydrazide

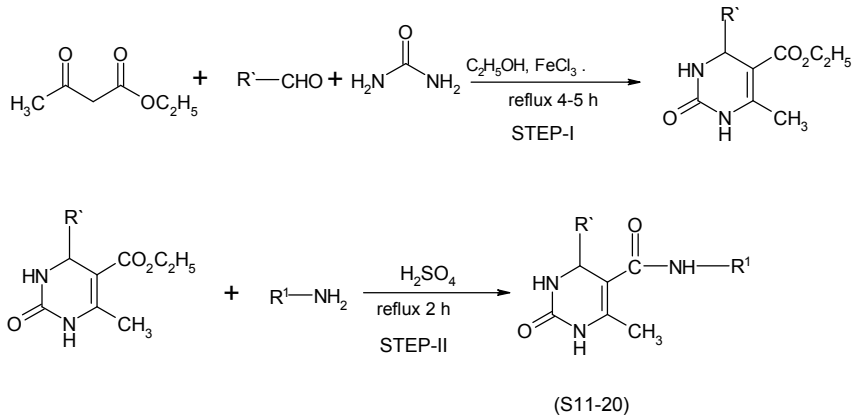

Fig. 2: Scheme for synthesis of 6-methyl-2-oxo-4-aryl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic acid arylamide

Table 1: Physical data of the tetrahydropyrimidine derivatives

					% calc. (% found)		
Comp	R'	Ar	R1	M. P	C	H	N
S1	4-OCH_3 C_6H_4	4-Cl C_6H_4	--	318-320	55.5 (55.4)	3.5 (3.6)	15.4 (15.4)
S2	4-OCH_3 C_6H_4	4-F C_6H_4	--	322-326	57.6 (57.5)	3.6 (3.7)	16.0 (16.2)
S3	4-OCH_3 C_6H_4	3,5-$(OCH_3)_2$ C_6H_4	--	286-290	57.6 (57.7)	4.4 (4.1)	14.6 (14.4)
S4	4-OCH_3 C_6H_4	2-furfural	--	266-270	55.7 (55.6)	3.6 (3.7)	17.1 (17.0)
S5	4-OCH_3 C_6H_4	4-$(CH_3)_2N$ C_6H_4	--	304-310	59.7 (59.7)	4.7 (4.6)	18.1 (18.2)
S6	4-OCH_3 C_6H_4	3,4,5-$(OCH_3)_3$ C_6H_4	--	298-300	56.5 (56.7)	4.5 (4.4)	13.7 (13.9)
S7	C_6H_5	4-Cl C_6H_4	--	320-324	56.6 (56.6)	3.3 (3.2)	16.5 (16.4)
S8	C_6H_5	4-OCH_3 C_6H_4	--	328-330	60.1 (60.0)	4.0 (4.1)	11.4 (11.4)
S9	C_6H_5	C_6H_5	--	306-308	61.6 (61.7)	3.8 (3.9)	17.9 (17.9)
S10	C_6H_5	4-CH_3 C_6H_4	--	311-312	62.5 (62.5)	4.2 (4.2)	17.3 (17.4)
S11	C_6H_5	--	C_6H_5	180-184	69.6 (69.7)	5.1 (5.1)	14.3 (14.2)
S12	C_6H_5	--	2-NO_2 C_6H_4	204-206	60.3 (60.3)	4.1 (4.0)	16.5 (16.5)
S13	C_6H_5	--	3- NO_2 C_6H_4	210-216	60.3 (60.2)	4.1 (4.0)	16.5 (16.4)
S14	C_6H_5	--	4- NO_2 C_6H_4	216-220	60.3 (60.2)	4.1 (4.1)	16.5 (16.4)
S15	C_6H_5	--	4-F C_6H_4	208-212	65.5 (65.6)	4.53 (4.52)	6.1 (6.1)
S16	4-OCH_3 C_6H_4	--	Phenyl	190-198	66.8 (66.8)	5.3 (5.2)	13.0 (13.0)
S17	4-OCH_3 C_6H_4	--	2-NO_2 C_6H_4	174-178	58.6 (58.7)	4.3 (4.3)	15.2 (15.1)
S18	4-OCH_3 C_6H_4	--	3- NO_2 C_6H_4	190-192	58.6 (58.7)	4.3 (4.4)	15.2 (15.1)
S19	4-OCH_3 C_6H_4	--	4- NO_2 C_6H_4	198-204	58.6 (58.6)	4.3 (4.4)	15.2 (15.2)
S20	4-OCH_3 C_6H_4	--	4-F C_6H_4	186-190	63.3 (63.3)	4.7 (4.7)	5.5 (5.6)

and tetrahydrofuran. The crude salt was stirred in water at approximately 80°C; stirring was continued until the clear solution is obtained. After cooling the solution was acidify by acetic acid and stirring was continued for 30 min. The deposited crystals thus formed were collected and washed well with water. The product was recrystalized from chloroform IR (KBr, cm^{-1}): 3220.54, (N-H stretching of secondary amine and amide group); 2229.31 (C≡N stretching of cyano group); 1662.2 (C=O stretching of amide group).

Step-II: Synthesis of [5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-3-yl] Ethyl Ethanoate (2A): A mixture of step-I product (0.01 mol) and ethyl bromoacetate (0.01 mol) in acetone (100 ml) containing potassium carbonate (0.01 mol) was heated under reflux on water bath for 6 hrs. White colored potassium salt of product obtained was dissolved in hot water. After cooling, the solution was acidified with dilute hydrochloric acid to precipitate the product. The product was filtered and washed with water. The crude product was dried and recrystallised from ethanol to obtain pure product. IR (KBr, cm^{-1}): 3266.2 (N-H stretching of secondary amine and amide group); 2225.45 (C≡N stretching of cyano group); 1739.48 (C=O stretching of ester group); 1654 (C=O stretching of amide group); 1050 (C-O stretching of ester group).

Step-III: Synthesis of [5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin- 3-yl] Ethanoic Acid Hydrazide (3A): A solution of step-II product (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (100 ml) was refluxed on water bath for 4 hrs. After cooling the reaction mixture the product obtained was filtered and dried in air. Product was recrystallised from ethanol to obtain pure product. IR (KBr, cm^{-1}): 3313.11, 3235.97, (NH_2 and NH stretching of hydrazide and amide group); 2217.74 (C≡N stretching of cyano group); 1673.91 (C=O stretching of amide group).

Step-IV: Synthesis of [5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-3-yl] Ethanoic Acid Arylidinehydrazide (S1-10): A mixture of step-III product (AH1 or BH1) (1 mmol) and aryl aldehyde (1 mmol) in ethanol (20 ml) was refluxed on water bath for 4hrs. After cooling the reaction mixture to room temperature, the obtained solid was filtered off and recrystallised from DMF to obtain pure product. IR (KBr, cm^{-1}), 3313.11, 3235.97 (NH_2 and NH stretching of hydrazide and amide group); 2217.74 (C≡N stretching of cyano group); 1673.91 (C=O stretching of amide group); 1600 (C=N of imino group). ^{1}H NMR (DMSO-d_6, δ /ppm), 2.50 (s, 2H, CH_2); 3.84 (s, 3H, OCH_3); 7.19 (d, 2H, arom); 7.48 (d, 2H, arom); 7.70 (s, 2H, NH_2); 9.9 (s, 2H, NH). MS (m/z (relative abundance, %)): 331.3 (M^+ 22.85); 301.33 (54.5%); 272.2 (100%); 258.4 (19.5%); 57 (47.51%).

Step-I: Synthesis of 3, 4-dihydropyrimidin-2(1H)-one: A solution of β-ketoester (10 mmol), appropriate aldehyde (10 mmol), urea (15 mmol), ferric chloride hexahydrate (2.5 mmol) and conc. hydrochloric acid (1-2 drops) in ethanol (20ml) was heated under reflux for 4 hours. After cooling, the reaction mixture was poured into crushed ice (100 gm). Stirring was continued for several minutes. The solid product was filtered, washed with cold water (2x50 ml) and a mixture of ethanol: water (1:1, 3x20 ml). The solid product was recrystallised from ethanol. IR (KBr, cm^{-1}), 3266.2 (N-H stretching of amide group); 1739.48 (C=O stretching of ester group); 1050 (C-O stretching of ester group).

Step-II: Synthesis of 6-methyl-2-oxo-4-aryl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic Acid Arylamide (S11-20): Aromatic amine (10 mmol) was added in flask containing step-I product (10 mmole) in ethanol (20ml). Then catalytic amount of conc. sulphuric acid (5 drops) was added. The mixture was refluxed for 2 hours. On cooling solid was separated out was filtered and recrystallised from ethanol.

IR (KBr, cm^{-1}), 3239.82, 3162.18 (N-H stretching of amide group); 1654.62 (C=O stretching of aromatic amide group). ^{1}H NMR (400 Hz, DMSO-d_6, δ /ppm), 2.23 (s, 3H, CH_3); 3.70 (s, 1H, CH); 5.08 (s, 1H, NH); 7.16-7.27 (m, 10H, arom); 7.65 (s, 1H, NH); 9.25 (s, 1H, NH). MS (m/z (relative abundance, %)): 307 (M^+ 12.8%); 187.2 (100%); 120.1(35%); 111.2(5.05%); 44.1(44%).

Anti-Inflammatory Activity: In-vitro testing [By Colorimetric COX (ovine) Inhibitor Screening Assay Kit]

The *in-vitro* COX-1 and COX-2 activity was performed as described previously [4]. The absorbance values are shown in Table 2.

Qsar Analysis [14-18]: The builder module of the Vlife MDS 3.5 was used to generate molecular models of series of chalcone derivatives. These were then energy-minimized using the Merck Molecular Force Field (MMFF) until the root mean square (rms) gradient reached value 0.001 kcal mol^{-1} A°. The physicochemical properties of each compound were specified using various descriptors, which delineate liphophillic, conformational, electronic,

Table 2: *In-vivo* and *In-vitro* COX-1 and COX-2 activity data of synthesized compounds

Compound	Absorbance (COX-1)**	Absorbance (COX-2)**	Selectivity Index
Background Well	0.271	0.254	--
100% Initial Activity Well	0.320	0.419	--
S1	0.386	0.332	1.473
S2	0.351	0.337	1.681
S3	0.365	0.3594	1.250
S4	0.337	0.396	1.233
S5	0.388	0.328	1.095
S6	0.374	0.348	1.150
S7	0.366	0.358	1.310
S8	0.340	0.391	1.083
S9	0.345	0.386	1.182
S10	0.364	0.361	1.365
S11	0.364	0.360	1.302
S12	0.336	0.397	1.238
S13	0.374	0.347	1.210
S14	0.446	0.253	1.926
S15	0.398	0.316	1.979
S16	0.368	0.355	1.796
S17	0.345	0.385	1.646
S18	0.379	0.340	1.229
S19	0.454	0.315	1.295
S20	0.406	0.305	1.991
Diclofenac	0.129	0.398	1.140

* Average of six readings (± S.D.)

** Average of three readings

Table 3: QSAR models generated for the in vitro and in vivo COX-2 and COX-1 inhibitory activity

Model No.	QSAR model	N	r^2	q^2	F value	Pred r^2	p statistics
A	ED_{80}= 3.2839 - 0.0352 (1.8348) kappa2-0.0760 (0.2339) IonizationPotential - 0.0341 (0.5521) QMDipoleMagnitude	16	0.9046	0.8645	61.6614	0.3575	<0.0001
B	IC_{80} = 2.3139 - 0.0026 (33.8957) SAHydrophilicArea - 0.0006 (4569.50) Quadrupole1 + 0.00001 (14.210) MomInertiaY	16	0.9161	0.8480	70.9562	0.8368	<0.0001
C	IC_{80} = -0.6781 + 2.6209(±0.3719) SKMostHydrophobic -0.0052(±0.0003) Quadrupole2 + 0.4013 (±0.1421) chi3Cluster	16	0.8359	0.7342	20.3710	0.4484	<0.001

Table 4: Predicted Activity obtained using selected QSAR equations along with Residuals

	In-vivo COX-2 Activity (pIC_{80})			In-vitro COX-2 Activity (pED_{80})			In-vitro COX-1 Activity (pIC_{80})		
Comp	Obs	Pred	Res	Obs	Pred	Res	Obs	Pred	Res
S1 t	2.015	2.021	-0.006	2.121	2.098	0.022	1.439	1.238	0.201
S2 t	1.971	2.004	-0.032	2.082	2.098	-0.016	1.752	1.651	0.101
S3	1.952	1.947	0.0054	2.064	2.071	-0.007	1.630	1.694	-0.064
S4	1.956	1.945	0.0104	2.089	2.090	-0.001	1.984	1.934	0.050
S5	2.006	2.003	0.0039	2.118	2.113	0.004	1.435	1.783	-0.348
S6	1.936	1.935	0.0007	2.051	2.042	0.008	1.577	1.616	-0.039
S7	2.025	2.034	-0.008	2.118	2.117	0.001	1.567	1.590	-0.023
S8	2.000	2.019	-0.018	2.084	2.105	-0.021	1.924	1.850	0.074

Table 4: Continue

	In-vivo COX-2 Activity (pIC_{80})			In-vitro COX-2 Activity (pED_{80})			In-vitro COX-1 Activity (pIC_{80})		
Comp	Obs	Pred	Res	Obs	Pred	Res	Obs	Pred	Res
S9 t	2.053	2.023	0.029	2.123	2.116	0.006	1.795	1.760	0.035
S10	2.037	2.027	0.0101	2.136	2.113	0.022	1.564	1.731	-0.167
S11	2.184	2.165	0.018	2.255	2.265	-0.010	1.446	1.739	-0.293
S12	2.115	2.133	-0.017	2.154	2.182	-0.028	1.945	1.828	0.117
S13	2.134	2.134	-0.000	2.212	2.193	0.018	1.417	1.219	0.198
S14 t	2.279	2.193	0.085	2.349	2.181	0.167	1.049	1.156	-0.107
S15	2.211	2.186	0.025	2.288	2.276	0.011	1.222	1.236	-0.014
S16	2.153	2.181	-0.028	2.22	2.241	-0.021	1.449	1.294	0.155
S17	2.089	2.152	-0.062	2.131	2.166	-0.035	1.787	1.777	0.010
S18	2.165	2.190	-0.024	2.185	2.151	0.033	1.414	1.661	-0.247
S19	2.250	2.178	0.0719	2.152	2.169	-0.017	1.057	1.137	-0.080
S20	2.181	2.167	0.0142	2.264	2.219	0.044	1.218	1.077	0.141

t Test set molecules

spatial, structural, thermodynamic and quantum mechanical information. Twenty compounds from this data set were divided into training and test sets, the former set consisting of 80% of the total compounds.

A relationship between independent (physicochemical properties) and dependent (Biological activity) variables were determined statistically using regression analysis. Linear regression is achieved by fitting a best-fit straight line to the data using the least squares method. The descriptors were selected having inter-correlation below 0.5. Quality of selected models was further ascertained to select the best model from cross-validated squared correlation coefficient (q^2). QSAR equations that have correlation coefficient which equal or exceed a preset value are reported. We specified 0.5 and 0.7 as the inter-correlation and correlation coefficient cutoff values, respectively. The selected models for various activities are shown in Table 3. To systematically assess a QSAR model, a reliable validation is required. Selected models having r^2 above 0.7 were checked for their external predictivity. The observed and the predicted values for *in-vivo* and *in-vitro* activity are shown in Table 4.

RESULTS AND DISCUSSION

In present work synthesis of some 1,2,3,4-tetrahydropyrimidine derivatives has been carried out. The reaction proceeds by Knoevenagel condensation and the condensed product reacts with thiourea to form an intermediate, which is subsequently cyclized by nucleophilic attack of nitrogen on carbonyl carbon. The step was confirmed due to absence of peaks at 1250 (C-O) ester and 1715 (C=O) aldehyde and presence of peak at 1662 (C=O) amide in the I.R. spectrum of the compound. The synthesized compounds were screened for *In vitro* COX-2 and COX-1 inhibitory activity to evaluate possible mode of action[19-21].

Interpretation of Model A: Model A was found best to express *in-vivo* COX-2 inhibitory activity as confirmed by validation of the model judging internal and external predictivity and other statistical terms like the pred r^2, F value and q^2. The variable terms in the equation show low correlation among themselves, indicating a lesser probability of chance correlation. As indicated in Table 3 the activity is dependent on kappa2, Ionization potential, QM Dipole Magnitude. The correlation plot of observed and predicted activity is shown in Fig. 3.

The kappa1 descriptor signifies first kappa shape index: $(n-1)^2 / m^2$. Calculated as $A(A-1)^2/({}^1P_i)^2$ where A is the number of non hydrogen atoms, ${}^1P_i$ is the count of single bond fragment. The shape descriptor is negatively correlated with the *in-vivo* COX-2 activity. This indicates that the increase in hydrogen atoms in the structure will lead to increase in activity. This may be due to increase in hydrogen bond interactions with the receptor by the hydrogen atoms attached by a single bond to the hetero atoms. This indicates that hydrogen bond interactions play important role in the activity.

The second parameter that is correlated with the activity is ionization potential. It is the indicative of energy required for the compound to ionize. The parameter is negatively correlated with the activity, meaning that ionization potential should be lesser for the compound so that charged interactions would be easily aggravated.

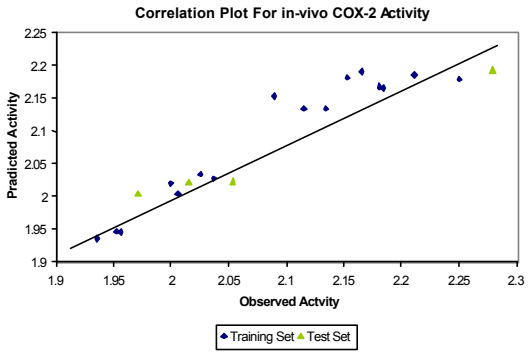

Fig. 3: Correlation graph of Observed and Predicted activity for in-vivo COX-2 inhibitory Activity

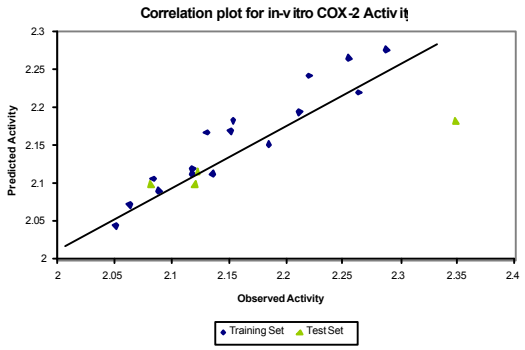

Fig. 4: Correlation graph of Observed and Predicted activity for in-vitro COX-2 inhibitory Activity

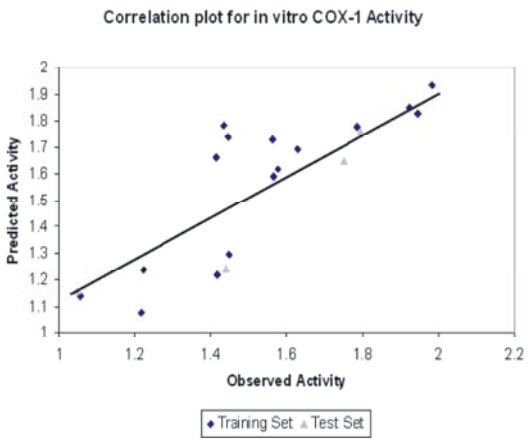

Fig. 5: Correlation graph of Observed and Predicted activity for in-vitro COX-1 inhibitory Activity

QMDipole magnitude is the total magnitude of induced dipole or a measure of charge distribution of the molecule.

Interpretation of Model B: Model B was found best to express *in vitro* COX-2 inhibitory activity as confirmed by validation of the model judging internal and external predictivity and other statistical terms like the pred r^2, F value and q^2. The variable terms in the equation show low correlation among themselves, indicating a lesser probability of chance correlation. As indicated in table 3. The activity is dependent on SAhydrophillic area, Quadrapole1, moment of inertia Y. The correlation plot of observed and predicted activity is shown in Fig. 4.

The SAhydrophillic area is one of the parameter contributing towards the activity. It represents vdW surface descriptor showing hydrophilic surface area calculated by Audry Method using SlogP. This parameter contributes negatively towards the activity, supporting the fact that hydrophilic interactions are not desirable at the COX-2 active site. The increase in number of hydrophobic moieties on the molecules will affect the activity positively, while polar groups like hydroxyl, methoxy will lead to decreased activity.

The second parameter quadrupole1 signifies magnitude of first tensor of quadrupole moments. The quadrupole moment similar to dipole moment defines the charge separation and the interactions with the receptor. The parameter is negatively correlated with the biological activity indicating that quadrupole moments if decreased they augment the activity.

The moment of inertia along Y axis is a steric parameter that is dependant on the spatial array of the aromatic ring in the synthesized compounds. The spatial arrangement also is necessary to study the interaction of the ligand with the receptor. The principle moment of inertia is positively correlated with the *in vitro* activity for COX-2 inhibition.

Interpretation of Model C: Model C was found best to express *in vitro* COX-1 inhibitory activity as confirmed by validation of the model judging internal and external predictivity and other statistical terms like the pred r^2, F value and q^2. The variable terms in the equation show low correlation among themselves, indicating a lesser probability of chance correlation. As indicated in Table 3 the activity is dependent on SKmosthydrophobic, Quadrapole2, Chi3Cluster. The correlation plot of observed and predicted activity is shown in Fig. 5.

The parameter SKmostHydrophobic area is contributing positively towards the COX-1 inhibition. This indicates increase in hydrophobic area of the molecule will increase the COX-1 inhibition activity.

The second parameter quadrupole 2 signifies magnitude of second tensor of quadrupole moments. The quadrupole moment similar to dipole moment defines the charge separation and the interactions with the receptor.

The parameter is negatively correlated with the biological activity indicating that quadrupole moments if decreased they augment the activity.

The third parameter chi3cluster signifies simple 3rd order cluster chi index in a compound. It is contributing positively towards activity, therefore Increasing the number of hydrogen atoms or ó electrons will augment the COX-1 inhibition.

CONCLUSION

QSAR analysis on a structurally diverse set of 1,2,3,4-tetrahydro pyrimidine compounds with *in vitro* COX-2 inhibitory activity was performed to find factors contributing to the activity and selectivity. Robust statistical parameters like p statistics and standard error of estimate, handled the physicochemical descriptors effectively. The generated models were analyzed and validated for their statistical significance and external prediction power. The variables in the equation reveal that thermodynamic, electronic, shape index and lipophillic, descriptors contribute significantly for COX-2 potency selectivity. The evaluation and comparison of QSAR models generated for achieving optimum COX-2 selectivity and potency provide understanding that the inhibition of the COX-2 enzyme by this diverse set of molecules may be noncovalent in nature and this leads to few significant conclusions:

- The presence of higher number of Hydrogen atoms along with higher electron doner species cans potentate *in vivo* COX-2 activity.
- The modulation of COX-2 activity can be achieved by decreasing the flexibility of the molecule in terms of lesser charge separation.
- Since more lipophilic character tends to favour *in-vivo* COX-2 activity, a molecule should be designed in a way so as to achieve a precise hydrophilic-lipophilic balance.
- Bulkiness of the molecule in desired range and specific conformation such that the pyrimidine ring and the side chain with carbonyl group are aligned at an angle of 90° to each other appear to be essential for the molecules to achieve optimum selectivity and anti-inflammatory activity.

In summary, results from the analysis of QSAR models connotes to the rationalization of the *in-vitro* COX-2 binding profiles, leading to the identification of structural and physicochemical requirements for enhancing reasonable affinity toward COX-2 in a qualitative and quantitative way. Moreover, the awareness and understanding of the descriptors influencing both the affinity and selectivity properties of these compounds could provide an opportunity to understand and optimize appropriate structural features of the ligand structures which correlate with the biological data. As a consequence, the outcome of this study could be useful as a guide for the further development of safer COX-2 inhibitors with high affinity and optimum selectivity towards the target of interest.

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REFERENCES

1. Kuhnert, N., 2000. Hundert Jahre Aspirin-Die Geschichte des wohl erfolgreichsten Medikaments des letzten Jahrhunderts. Pharmazie in unserer Zeit, 1: 32-39. DOI: 10.1002/(SICI)1615-1003(200001).
2. Marnett, L.J. and A.S. Kalgutkar, 1999. Cyclooxygenase 2 inhibitors: discovery, selectivity and the future. Trends in Pharmacological. Sci., 20: 465-469.
3. Allison, M.C., A.G. Howatson, C.J. Torrance, F.D. Lee and R.L. Russel, 1992. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. New England J. Med., 327: 749-754.
4. Zambre, A.P., A.L. Ganure, D.B. Shinde and V.M. Kulkarni, 2007. Perspective Assessment of COX-1 and COX-2 Selectivity of Nonsteroidal Anti-Inflammatory Drugs from Clinical Practice: Use of Genetic Function Approximation. J. Chemical Information and Modelling, 47(2): 5-643. DOI: 10.1021/ci6004367
5. Kumar, B., B.Kaur, J. Kaur, A. Parmar, R. Anand and H. Kumar, 2002. Thermal/microwave assisted synthesis of substituted tetrahydropyrimidines as potent calcium channel blockers. Indian J. Chemistry, 41B: 1526-1527.
6. Schneider, P., P. Hawser and K. Islam, 2003. Iclaprim, a novel diaminopyrimidine with potent activity on trimethoprim sensitive and resistant bacteria. Bioorganic Medicinal Chemistry Letters, 13: 4217-4221. DOI:10.1016/j.bmcl.2003.07.023

7. Vlietinck, A.J., V.J. Ram and D.A. Berghe, 1984. 5-Cyano-6-aryluracil and 2-thiouracil derivatives as potential chemotherapeutic agents. IV. Journal of Heterocyclic Chemistry, 21: 1307-1312. DOI: 10.1002/jhet.5570210513
8. Summa, V., A. Petrocchi, V.G. Matassa, M. Taliani, R. Laufer and R.D. Francesco, 2004. HCV NS5b RNA-Dependent RNA Polymerase Inhibitors: From α,γ-Diketoacids to 4,5-Dihydroxypyrimidine- or 3-Methyl-5- hydroxypyrimidinonecarboxylic Acids. Design and Synthesis. J. Medicinal Chemistry, 47: 5336-5339. DOI: 10.1021/jm0494669
9. Hockova, D., A. Holy, R. Snoeck and E.D. Clercq, 2003. 5-Substituted-2,4-diamino-6-[2-(phosphonomethoxy) ethoxy] pyrimidines Acyclic Nucleoside Phosphonate Analogues with Antiviral Activity. J. Medicinal Chemistry, 46: 5064-5073. DOI: 10.1021/jm030932o
10. Baettie, J.F., G.A. Breault, P.A. Ellston, P.J. Jewsbury, C.J. Midgley, R.T. Naven, C.A. Minshulland and J.A. Tucker, 2003. Cyclin-dependent kinase 4 inhibitors as a treatment for cancer. Part 1: identification and optimisation of substituted 4,6-Bis anilino pyrimidines, Bioorganic Medicinal Chemistry Letters, 13: 2955-2960. DOI:10.1016/S0960-894X(03)00202-6.
11. Richardson, M.L., K.A. Croughton, C.S. Matthews and F.G. Stevence, 2004. Structural Studies on Bioactive Compounds. 39.1 Biological Consequences of the Structural Modification of DHFR-Inhibitory 2,4-Diamino-6-(4-substituted benzylamino-3-nitrophenyl)-6-ethylpyrimidines (‘benzoprims'), J. Medicinal Chemistry, 23: 4105-4108. DOI: 10.1021/jm040785.
12. Bahekar, S.S. and D.B. Shide, 2003. Synthesis and anti-inflammatory activity of some [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidine-5-yl]-acetic acid derivatives. Acta Pharmaceutica, 53: 223-229.
13. Kambe, S., K. Saito and H. Kishi, 1979. A One-Step Synthesis of 4-Oxo-2-thioxopyrimidine Derivatives by the Ternary Condensation of Ethyl Cyanoacetate, Aldehydes and Thiourea. Synthesis, 4: 287-288.
14. Ibezim, E.C., P.R. Duchowicz, N.E. Ibezim, L.M. Mullen, I.V. Onyishi, S.A. Brown and E.A. Castro, 2009. Computer-Aided Linear Modeling Employing QSAR for Drug Discovery. African J. Basic and Applied Sci., 1 (3-4): 76-82.
15. Sharma, M.C. and D.V. Kohli, 2011. Predicting Alkylbenzimidazole Derivatives as Angiotensin II Receptor Antagonists: 3D QSAR by kNN-MFA Approach. Advances in Biological Res., 5(3): 161-169.
16. Sharma, M.C. and D.V. Kohli, 2011. 3D QSAR Studies of Substituted-4(3H) Quinazolinones Derivatives as Angiotensin II Receptor Antagonists European J. Applied Sci., 3(1): 15-23.
17. Sharma, M.C. and D.V. Kohli, 2011. QSAR Study on Sulfonylcarbamare Derivatives: An Insight into the structural Requirement for the Angiotensin II receptor Antagonist European J. Applied Sci., 3(1): 09-14.
18. Sharma, M.C. and D.V. Kohli, 2011. Exploration of Quantitative Structure Activity Relationship Studies on a Series of Substituted Quinazolinones as Angiotensin II AT1 Receptor Anagonists World Applied Sciences J., 12(11): 2111-2119.
19. Sharma, S., M.C. Sharma and A.D. Sharma, 2010. Quantitative structure-activity relationship analysis of some 2-substituted halogenbenzimidazoles analogues using computer-aided drug designing technique. J. Chemical and Pharmaceutical Res., 2(2): 357-365.
20. Khistia, N.A. and S.V. Gandhib, 2011. Pharmacophore optimization of selective p38 map kinase Inhibitors as potential anti-inflammatory agents using Molecular modeling studies. International J. PharmacyandTechnol., 3 : 2323-2342.
21. Vogel, H.G., 2002. In; Drug Discovery and Evaluation-Pharmacological Assays, 2nd Edn. Springer-Verlag Publication, New York, pp: 670.